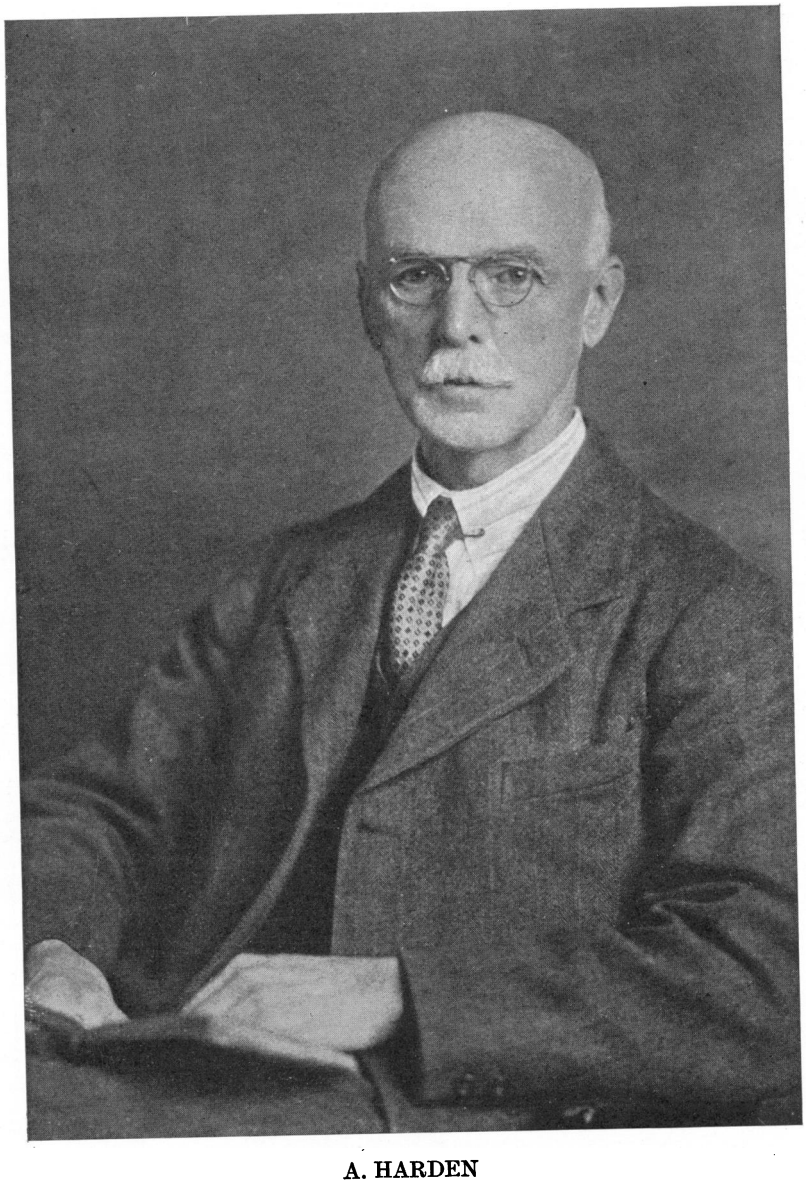

A. HARDEN
(1865-1940)

OBITUARY NOTICES

ARTHUR HARDEN

(1865–1940)

SIR ARTHUR HARDEN, founder-member of the Biochemical Society and for 25 years editor of its *Journal*, died on 17 June 1940 at his home at Bourne End.

Arthur Harden was born in Manchester on 12 October 1865. He was the only son of Albert Tyas Harden, a Manchester business man who had married Miss Eliza MacAlister of Paisley. The family, consisting of Arthur and his sisters, was brought up in a somewhat austere nonconformist atmosphere, like the Scottish Presbyterians, abjuring the theatre and regarding Christmas almost as a pagan festival. At the age of 7 years Arthur was sent to a private school kept by Dr Ernest Adam in Victoria Park, and four years later in 1877 he went on to the Tettenhall College in Staffordshire where he stayed until he was 16, waiting an extra term in order to qualify for the London matriculation. In January 1882, he entered Owens College, Manchester, and studied chemistry under Prof. Roscoe, then at the height of his fame as a teacher. In 1885 he graduated in the Victoria University with first class honours in chemistry and a year later was awarded the Dalton scholarship. It was J. B. Cohen, to whose stimulating teaching Harden doubtless owed much, who suggested the subject of Harden's first research, 'The action of silicon tetrachloride on aromatic amide-compounds', and in the following year the results of this investigation were published in the *Transactions of the Chemical Society* [1886]. From Manchester he proceeded to Erlangen, and under the direction of Otto Fischer prepared β-nitroso-α-naphthylamine and investigated its properties. Having been awarded the degree of Ph.D. he returned to Manchester and there became junior and later senior lecturer and demonstrator under Prof. H. B. Dixon who had succeeded Sir Henry Roscoe as Professor of Chemistry. During part of this time Harden shared with (Sir Philip) Hartog the laboratory teaching, at first in the large qualitative and then in the quantitative laboratory, and for some years he lectured to the Honours students on the history of chemistry, a subject in which he was greatly interested. With characteristic thoroughness he traced out members of the Dalton family and obtained from them information about Dalton's family and procured a photograph of Dalton's birthplace. This interest was shared by Roscoe: together Harden and he studied the note-books and arrived at the conclusion that it was Dalton's investigation of the relations governing the diffusion of gases that led him to formulate his atomic principles; these views were published in two papers on the genesis of Dalton's Atomic Theory [*Phil. Mag.* 1897, p. 153; *Z. phys. Chem.* 1897, **22**, 243], and were also expanded in a book entitled *A New View of the Genesis of Dalton's Atomic Theory*. Harden's interest in Dalton remained, and in 1915, with H. F. Coward, he communicated to the Manchester Literary and Philosophical Society a description of some of the lecture sheets with which Dalton used to illustrate his lectures and which had recently been discovered in the rooms of the Society.

In 1895, Roscoe, stimulated by an article on the teaching of science contributed by H. E. Armstrong to *Nature*, suggested that Harden should collaborate with him in a book for advanced students, and the outcome of this was a text-book to fulfil the needs of students for the higher South Kensington Examination.

In collaboration with F. C. Garrett, a book on *Practical Organic Chemistry* was written, planned to accompany Perkins's *Organic Chemistry*. At Roscoe's request, Harden also undertook the work of revising and editing a new edition of Roscoe and Schorlemmer's *Treatise on Inorganic Chemistry*; this was carried out in collaboration with Colman, a fellow-student who remained throughout one of Harden's closest friends, and the experience must have served as valuable training for the editorial work which was to occupy so much time in his later life. As at this time the salary of a senior lecturer in chemistry at Owens College was only £150 a year, the money obtained by his literary work must have formed a useful addition to the salary.

During these nine years of lecturing and teaching in Manchester, Harden seems to have been chiefly interested in his teaching and literary work. He believed that teaching was the primary duty of a demonstrator and that it was unfair to grumble because the student had not already learnt what the demonstrator was paid to teach him. The Department was then supplying a steady stream of chemists for the expanding industries of the north, and Harden made it his business to become acquainted with their technical problems and often advised firms who had met with some difficulty or other. He published only two papers based on experimental work; both appeared in the *Transactions of the Manchester Literary and Philosophical Society*, one with W. Haldane Gee [1891] on a new form of stereometer, and one on the composition of some iron and bronze implements which had been found by Prof. Flinders Petrie, then Professor of Geology at Manchester [1897]. Harden obtained the consent of Prof. Otto Fischer to continue the work on nitroso-compounds, but nothing further appeared on this subject. He began experiments on the combination of carbon monoxide and chlorine, with a view to studying the phenomenon of photochemical induction, a subject in which Dixon was especially interested; this work was carried out in collaboration with Dyson, but the results were not published until 1903, six years after Harden had left Manchester. It seems therefore that up to the time he left Manchester at the age of 32, Harden had given no indication of any marked interest in scientific research. He had applied for the posts of Principal at the Wandsworth Technical Institute and of Inspector under the Science and Arts Department at South Kensington: fortunately, both these applications were refused, the former on the ground that his training was too highly specialized and the latter on the ground of his youth.

In 1897, Sir Henry Roscoe was treasurer of the British Institute of Preventive Medicine, which had laboratories in Great Russell Street. It was an Institute which fulfilled various functions. It held classes for students of Public Health in bacteriology and chemistry, carried out bacteriological and chemical analyses, the latter mainly water analyses for municipal departments, and the members of the staff also carried out scientific research.

It was at the suggestion of Sir Henry Roscoe and largely because he had proved himself a successful teacher and lecturer that Harden was appointed a member of the Institute staff. Shortly afterwards, however, the Medical Schools themselves introduced teaching in bacteriology, and the classes at the British Institute were discontinued. In May 1898 the British Institute was transferred to a new building at Chelsea, and later in the year its title was changed to the Jenner Institute of Preventive Medicine.

At the Jenner Institute, Harden was associated with Dr Allan Macfadyen who was in charge of the bacteriological department, and it was at his suggestion that Harden undertook the investigation of the bacterial fermentation of sugars. Originally the object of the work was to find diagnostic tests for the differentiation

of varieties of *Bact. coli commune* and closely related organisms. It was Harden's introduction to the science of biochemistry, and his interest in the nature of bacterial fermentation was maintained during the rest of his life. His first paper on the action of *Bact. coli commune* and allied organisms appeared in the *Transactions of the Jenner Institute* for 1899, and later was extended in the *Transactions of the Chemical Society* [1901, **19**, 610]. He estimated the decomposition products of glucose, compared them with those from mannitol, and established that the two terminal alcohol groups were the source of the acetic acid and alcohol formed in the reaction. *Bacillus lactis aerogenes* was also studied, and the ratio of alcohol to acetic acid produced was shown to serve as a possible basis for the differentiation of these two organisms [*J. Hyg., Camb.*, 1905, **5**, 488]. Two substances, hitherto unknown as products of bacterial action on sugars, 2:3-butylene glycol and acetyl methyl carbinol, were identified as characteristic of *B. lactis aerogenes* [Harden & Walpole, *Proc. roy. Soc.* B, 1906, **77**, 488], and acetyl methyl carbinol was shown to be the substance responsible for the colour test described by Vosges & Proskauer [*Proc. roy. Soc.* B, 1906, **77**, 424]. The bacterial formation of this substance and of the corresponding butylene glycol was followed up in two papers with D. Norris [*Proc. roy. Soc.* B, 1912, **84**, 492; 1912, **85**, 73] and the atomic grouping in proteins which was responsible for the diacetyl test determined [*J. Physiol.* 1911, **42**, 332]. A final paper on this subject appeared dealing with the chemical action on glucose of a variety of *Bact. coli commune* (Escherich) obtained by cultivation in presence of chloroacetate [Penfold & Harden, *Proc. roy. Soc.* B, 1912, **85**, 415].

It was in 1897, the year in which Harden was appointed to his post at the British Institute, that Buchner had published his epoch-making discovery that the living cell was not essential to the process of fermentation and had established that cell-free yeast juice was able to bring about the decomposition of sugar, though the rate of fermentation was greatly diminished. The attention of both bacteriologists and chemists was now focused on yeast, and experiments were started at the Jenner Institute to obtain a yeast antibody. Harden's interest in the subject was aroused, and in 1901 a paper appeared in collaboration with Rowland [*Trans. Chem. Soc.* **79**, 1227] on the autofermentation and liquefaction of yeast. The effect of temperature in hastening liquefaction was studied, and the oxygen absorbed and carbonic acid set free during the process were measured; the conclusion was drawn that the alcoholic fermentation in the liquefied yeast corresponded with the autofermentation of the glycogen it contained, the proportion of alcohol to CO_2 evolved being 1 : 1. This paper is also interesting as being carried out with the assistance of Mr W. J. Young, whose collaboration was to prove so fruitful during the next ten years. With Young, Harden then examined the preparation of yeast glycogen, and made a careful comparison of its properties with those of the glycogens obtained from the oyster and the rabbit [*Trans. Chem. Soc.* 1902, **81**, 1224], and then in 1903 appeared the record of the effect of blood serum in increasing the alcoholic fermentation of yeast juice, the elucidation of which phenomenon was to lead to such fruitful results [*Ber. dtsch. chem. Ges.* 1903, **36**, 715]. The observation that not only did yeast juice exercise no proteolytic effect on rabbit and horse sera but that the latter inhibited the autoproteolysis of the yeast was unexpected, and led to the addition of serum to a mixture of glucose and yeast juice with the striking result that there was an increased evolution of CO_2. The next important step was the discovery that boiled yeast juice though itself incapable of producing fermentation, when added to a fermenting mixture of glucose and yeast juice greatly increased the amount of CO_2 evolved. It had previously been suggested that the

rapid loss of fermentative power characteristic of a yeast juice fermentation was due to the destruction of the alcoholic ferment by a proteolytic enzyme, but Harden and Young attributed the stimulating effect of the boiled yeast juice to an increased activity of the alcoholic ferment and not to the diminution of the proteolytic effect.

In order to follow the progress of the fermentation, Harden and Young measured the evolution of CO_2: they were thus able to follow the rate of the reaction during the whole course of the experiment and to learn much that would have been missed had they dealt only with the end products of the reaction.

In 1903, the Jenner Institute again changed its name and became the Lister Institute, and Dr C. J. Martin was appointed as its Director. In working on the antitoxin of snake venom, Martin had devised a gelatin filter which would work under high pressure and which had been applied by him to the separation of high-molecular colloids from crystalloids. He now suggested its application to the problem of separating the yeast juice into its constituents, and by its use Harden and Young effected the separation into a clear solution and an oily residue. Separately both of these solutions were inactive: together their activity was almost equal to that of the original juice [*Proc. physiol. Soc.* 1904, 32]. A further paper dealt with the differences between the results obtained by Macfadyen, Rowland and Morris and by Buchner in their respective investigations on yeast press juice, and the explanation was found in the differences between the bottom and top yeasts which had been used in the two investigations. In this paper [*Ber. dtsch. chem. Ges.* 1904, **37**, 1052] it was stressed that in both cases a considerable proportion of the sugar was converted into non-reducing substances which were later to be accounted for by the conversion of sugar into polysaccharides [*Biochem. J.* 1913, **7**, 630]. A lecture given to members of the Institute of Brewing in which these researches were described aroused much interest [*J. Inst. Brew.* 1905, **11**, 1].

Between the years 1906 and 1911, Harden and Young contributed six papers to the *Proceedings of the Royal Society* in which were described their classical researches on alcoholic fermentation.

Starting from the fact that the fermentation of glucose by yeast juice was increased by the addition of boiled filtered yeast juice, they showed that the boiled juice could be replaced by the precipitate thrown down by the addition of alcohol to boiled yeast juice, by the liquid formed by autoplasmolysis of yeast, or by the liquid formed by boiling Buchner's acetone-killed yeast with water. By means of the Martin gelatin filter, the juice was separated into two parts, an oily residue, later obtained as a dry powder, and a dialysate containing a thermostable substance. The addition of boiled filtered juice to a mixture of glucose and yeast juice produced a rapid initial evolution of CO_2 gradually diminishing to constant rate; the 'extra' CO_2 was directly proportional to the volume of boiled juice added, and one molecular proportion of CO_2 was given off for each atom of phosphorus added. The fermentation rate then diminished more slowly and continued for a longer period than without the addition of boiled juice. The phosphate entering into the reaction was changed into a form no longer precipitable by the magnesia mixture, yet a solution of soluble phosphate could not replace the boiled juice. Another factor, for which Harden adopted Bertrand's term of 'co-ferment', was also present, both phosphate and co-ferment co-operating with the zymase of the unboiled juice to produce fermentation.

Disappearance either of the ferment or of the co-ferment brought the fermentation to an end, but normally the co-ferment was the first to be used up, dis-

appearing, however, less rapidly in the presence of glucose than in its absence. Addition of phosphate produced the decomposition of an equivalent amount of glucose and a greater total amount of fermentation.

The change of the phosphate to a form no longer precipitable by magnesia mixture was explained when Young [*Proc. Chem. Soc.* 1907, 65] isolated the barium salt of a hexosediphosphoric acid and the demonstration of the slow conversion of the hexosediphosphate into hexose and phosphate by yeast juice was another important step. The equations representing the reactions were given as:

(1) $2C_6H_{12}O_6+2R_2HPO_4=2CO_2+2C_2H_6O+C_6H_{10}O_4(PO_4R_2)_2+2H_2O$,

(2) $C_6H_{10}O_4(PO_4R_2)_2+2H_2O=C_6H_{12}O_6+2R_2HPO_4$.

The co-ferment was regarded as a substance containing a phosphoric group united with a group of unknown composition by means of which the phosphate group was passed on to the sugar molecule and a new phosphate group taken up.

The presence of phosphate inhibited the enzymic decomposition of the hexosediphosphate; an optimum concentration of phosphate produced a maximum initial rate of fermentation and further increase of phosphate diminished the rate of fermentation.

The behaviour of mannose and fructose threw further light on the constitution of the hexosephosphate. Mannose was fermented as rapidly as and fructose more rapidly than glucose. The rates of fermentation of all three sugars were accelerated by phosphate, but that of fructose was double that of glucose or mannose and it was much less rapidly inhibited by the further addition of phosphate. The hexosediphosphates prepared from these three sugars were identical and the quantitative relations were expressed by the same equations. Young suggested that the hexosephosphate was probably derived from the enolic form common to the three sugars, though he did not ignore the possibility that the two molecules of sugar were broken down into smaller groups and hexosephosphate resynthesized from these [*Proc. roy. Soc.* B, 1909, **81**, 528].

After suitable 'training' of the yeast, galactose was also fermented and from this also an active juice was prepared [Harden & Norris, *Proc. roy. Soc.* B, 1910, **82**, 645].

Naturally there followed a period of controversy. Buchner's suggestion that lactic acid was an intermediate in sugar fermentation was rejected by Harden, a view in which Buchner eventually concurred though unfortunately not before it had been widely accepted by biologists. Iwanoff claimed to have isolated a triosephosphate giving an osazone (M.P. 128) similar to one prepared by Lebedeff from the oxidation products of glycerol. According to Iwanoff, the formation of hexosephosphate preceded the alcoholic fermentation, and the amount of fermentation should be proportional to the amount of hexosephosphate decomposed. Harden and Young did not at first accept this view, but the existence of Iwanoff's triosephosphoric acid was confirmed in 1907 by Young who isolated it as a lead salt. No attempt seems, however, to have been made by Harden to introduce the triosephosphate into his equations, and its significance does not appear to have been appreciated. Lebedeff, from the analysis of the osazone, regarded the hexose ester as a monophosphate and challenged the individuality of the hexosediphosphate, suggesting that it was an amorphous mixture of hexosemonophosphate and inorganic phosphate, a suggestion disproved by the discoverers, for Young found that phosphoric acid was liberated when the osazone was formed. Dihydroxyacetone was suggested by Lebedeff as an intermediate stage of glucose fermentation and for a time replaced lactic acid as favourite until it was shown by Harden to be more slowly fermented than sugar;

when added to a fermenting mixture of glucose and yeast juice dihydroxyacetone did not increase fermentation.

Arsenates added to the fermenting mixtures were found greatly to accelerate the production of CO_2 and alcohol, but Harden and Young clearly recognized that arsenate could not be substituted for phosphate and that it played some entirely different role in stimulating fermentation.

For about 25 years the nature of the coenzyme provoked much discussion and research. Harden and Young had correctly described it as a body in which phosphate was combined with some other group which was able to take up and to pass on the phosphate group, but it was only in 1937 that the work of Warburg and of Euler successfully established its structure as that of adenine pyridine diphosphonucleotide.

The partnership of Harden and Young was now broken. Young left for Australia on his appointment as Biochemist to the Australian Institute of Tropical Medicine at Townsville in 1912, and Robert Robison was appointed as his successor. In 1914 the new collaborators announced their discovery of a monohexosephosphate accompanying the hexosediphosphate in yeast; it could be separated by precipitation with basic lead acetate after the diphosphate had been removed by precipitation with normal lead acetate, and was differentiated from the latter by the greater solubility of its barium salt.

When it was discovered that the products of fermentation contained not only a hexosediphosphate but also a monophosphate, in collaboration with F. R. Henley [Lord Henley] Harden again returned to the examination of his equations [*Biochem. J.* 1920, **14**, 642; 1921, **15**, 175] and endeavoured to reconcile them with the presence of both a mono- and a di-phosphate, but they were forced to the conclusion that when a large proportion of monophosphate existed in the solution, the equations could not be applied. The only quantitative relation that could be clearly established was that, during the course of the fermentation, for each molecule of phosphate esterified approximately one molecule of CO_2 was evolved. If dried yeast was used the ratio was slightly greater than unity, with yeast juice or zymin it was somewhat less. The proportions of the mono- and di-phosphates in the solution, however, varied enormously, in the extreme cases consisting of 96% diphosphate or of 86% monophosphate. Obviously the relations of these two intermediate substances were not clearly understood, and it was not until the work of Meyerhof and his colleagues had established that the monophosphate was the first product of phosphorylation and the hexosediphosphate was formed by the phosphorylation of the monophosphate and then converted into two molecules of triosephosphate that any attempt to express the course of the fermentation by equations could have been successful. Harden's equations represented the simultaneous decomposition of two molecules of hexose, only one of which became phosphorylated. He did not for some time accept the view that all hexose molecules became phosphorylated before decomposition took place.

Subsequently it was shown by Macfarlane [*Biochem. J.* 1930, **24**, 1051], working in Harden's laboratory, that an autolysed solution of dried yeast which was incapable of fermenting glucose, even after the addition of the coenzyme, could break down hexosediphosphate producing inorganic phosphate and CO_2. The existence of a definite phosphatase acting on the hexosediphosphate was therefore established. When coenzyme and arsenate were added, the decomposition of the hexosediphosphate was extremely rapid, and CO_2 and inorganic phosphate appeared as final products of the decomposition. It was the breakdown of the hexosediphosphate that was stimulated by the presence of arsenate.

Of the great fall in fermentative activity which occurred when fresh yeast was converted into yeast juice, 80% was found to occur during the process of grinding, and it was during the same period that the yeast acquired the power of responding to phosphates. It was therefore the phosphatase which was affected [Harden & Macfarlane, *Biochem. J.* 1930, **24**, 243].

The nature of the enzymes in yeast and their method of action was investigated by Harden and his colleagues in a long series of researches which were more especially concerned with the enzymes existing in the dried yeast preparations.

He confirmed Neuberg's discovery [Neuberg & Hildesheimer, *Biochem. Z.* **31**, 170] of the existence of the enzyme carboxylase in dried yeast which split pyruvic acid into CO_2 and acetaldehyde and showed that as this reaction took place after the coenzyme had been completely washed away, it was independent of the presence of the coenzyme [*Biochem. J.* 1913, **7**, 214]. The reducing power of zymin or dried yeast, on the other hand, was removed by washing but could be restored by the addition of the boiled washings. Certain aldehydes also restored the reducing power and therefore had the property of acting as oxygen acceptors. Similar experiments carried out with washed rabbit muscle showed that here the addition of either lactic acid or acetaldehyde restored the reducing power [Harden & Norris, *Biochem. J.* 1914, **8**, 100; 1915, **9**, 330]. Evidence was obtained of the existence of a peroxidase in fresh yeast, the activity of which was lost when the yeast was dried for 17 hr. at 37°, but was restored by washing. Washing the dried yeast removed the activity of the invertase and maltase, whereas that of the catalase was not affected [Harden & Zilva, *Biochem. J.* 1914, **8**, 222]. Harden also showed that the presence of inorganic salts exercised a marked influence on the autofermentation of yeast [Harden & Paine, *Proc. roy. Soc.* B, 1911, **84**, 448], since all dissolved substances which plasmolysed the yeast cell caused also a large increase in the rate of autofermentation. The study of the addition of substances capable of acting as oxygen acceptors led to a surprising result. Washed zymin in the presence of a suitable concentration of sodium phosphate was activated by sodium pyruvate but not by the acetaldehyde into which the pyruvate was decarboxylated by yeast; if, however, the sodium phosphate were replaced by the potassium salt, the acetaldehyde also acted as an activator. Obviously the sodium and potassium ions were not interchangeable, and the potassium ion played some specific role [*Biochem. J.* 1917, **11**, 64]. On the other hand, when the fermentation of fructose or glucose by dried preparations of yeast was examined, it was found to be equally depressed by the addition of sodium or potassium chloride, the effect of the sulphates being somewhat greater. This effect was traced to the action of the salts on the hexosephosphate reaction. Potassium phosphate also produced a depressing effect, but here the depressing effect could be counteracted by the addition of acetaldehyde to the solution [Harden & Henley, *Biochem. J.* 1921, **15**, 312].

When dried yeast preparations acted in the presence of a large volume of sugar solution there was a considerable induction period before rapid fermentation set in, this period being reduced by the addition of various salts, both organic and inorganic. Sodium arsenate alone prolonged the time of the induction period without any toxic effect on the subsequent fermentation [Harden, *Biochem. J.* 1925, **19**, 477; Harden & Macfarlane, 1928, **22**, 786]. It was not possible to explain satisfactorily the effect of the ions, but the complexity of the process became ever more apparent.

War broke out in 1914, and from 1915 during the absence of the Director on military duties, Harden acted as Deputy-Director of the Lister Institute. About

three years previously, at the suggestion of Dr C. J. Martin, work on the nature of the substance responsible for curing the polyneuritis of pigeons had been carried out at the Lister Institute by Funk and Cooper, and in 1917, when the subject had become one of great practical importance, Harden in collaboration with Zilva carried out a series of researches on the antineuritic and antiscorbutic vitamins. They established that neither α-hydroxypyridine nor adenine was the active agent in curing beriberi as had been previously suggested [*Biochem. J.* 1917, **11**, 172]; they differentiated clearly between these two water-soluble factors showing that the antineuritic but not the antiscorbutic substance was adsorbed by fuller's earth [*Biochem. J.* 1918, **12**, 93]. A considerable concentration of the antiscorbutic factor was achieved by removing the organic acids of lemon juice, leaving a decitrated residue of much increased potency [*Biochem. J.* 1918, **12**, 250], and in collaboration with Dr Still the clinical effect of this product was studied. Harden and Zilva were the first to recognize clearly that scurvy was a disease brought about by the dietetic deficiency of a specific substance and not, as had been suggested by MacCollum and Pitz, by a generally unwholesome diet. The susceptibility of this vitamin to alkalinity was noted [*Lancet*, 7 Sept. 1918]: the antineuritic and antiscorbutic principles were shown to be lacking in ale, stout and fine beer. The antiscorbutic requirements of the monkey were determined [*J. Path. Bact.* 1919, **22**, 246; *Biochem. J.* 1920, **14**, 171; *Lancet*, 1919, **2**, 7, 780], and the antineuritic substance shown to be necessary for the growth of frogs [*Biochem. J.* 1920, **14**, 263]. With Bacot, *Drosophila* was shown to need B but not the C vitamin [*Biochem. J.* 1922, **16**, 48], and evidence was given establishing the biological synthesis of vitamin B by yeast [*Biochem. J.* 1921, **15**, 438]. With Robison, the practical effect on their vitamin C content of heating and storing fruit juices was investigated and results of practical importance obtained which were published in the *Journal of the R.A.M.C.* [*Biochem. J.* 1920, **14**, 171]. A Friday evening lecture on this subject was given at the Royal Institution on 28 April 1922.

During this period Harden did valuable work as a member of the Accessory Food Factors Commmittee set up by the Medical Research Council and was the editor of their Report on this subject.

The chemist who brings about chemical transformations in the laboratory relies largely on splitting off and recombining the elements of water. Here he can work at high temperatures and with powerful reagents. In the laboratory of the living organism the reactions must be brought about at almost constant temperature and with no violent changes of reaction. It is the great achievement of Harden and his colleagues to have discovered that the process of phosphorylation and dephosphorylation forms the basis of the mechanism by which carbohydrate is broken down in the living organism. They elucidated the manner in which this process was brought about, since they discovered that a definite substance, 'the coenzyme', existed and suggested that its function was to take up and pass on the phosphate radical. Their evidence of phosphorylation was indisputable since they isolated two intermediate compounds in which phosphate was bound to the hexose molecule, the 1:6-hexosediphosphate and the 6-hexosemonophosphate. Evidence of the process of dephosphorylation was given when they described the effects of a specific enzyme, a hexosediphosphatase, breaking down the hexosediphosphate with liberation of free phosphoric acid. The foundations of carbohydrate biochemistry were indeed well and truly laid.

Harden's power of accurate observation and of clear thinking enabled him to find his way in this new and complicated field so that although there remained many steps to fill in, there was little to withdraw. He realized early the com-

plexity of the process himself, describing the yeast cell as provided with a regular army of enzymes and coenzymes.

This work of Harden has already had two remarkable developments. It was applied to unravel the chemistry of the breakdown of carbohydrate in muscle by Embden in 1913 and later by Meyerhof and his colleagues, and as the result the steps by which glycogen is converted into lactic acid in the animal organism have been elucidated. From his work with Harden on yeast monophosphate Robison was led to his studies on the nature of ossification, where again the process of phosphorylation and dephosphorylation was found to be involved.

Recognition of the importance of his researches was not long delayed. Harden was elected to the Fellowship of the Royal Society in 1909. He was made Head of the newly formed Department of Biochemistry of the Lister Institute in 1907 and Professor of Biochemistry in the University of London in 1912. In 1929 he shared with Euler the Nobel prize for biochemistry. He was awarded the Davy Medal of the Royal Society in 1935 and in 1936 received the honour of knighthood. The Institute of Brewing made him an Honorary Member, the Universities of Manchester, Liverpool and Athens conferred Honorary Degrees upon him, and the Kaiserlich Leopold Deutsche Akademie der Naturforsche, Halle, elected him to its membership. The award of the Nobel prize gave him much pleasure and he enjoyed greatly the Stockholm visit. It was fitting that at the same ceremony Sir Frederick Gowland Hopkins shared with Eijkman the Nobel prize for Medicine, and that the two men who had done so much to build up the science of biochemistry should thus have been honoured together.

At the Lister Institute there was little opportunity for Harden to exercise his undoubted gift for teaching, but for many years one evening a week was devoted to a class in microbiology, at the Sir John Cass Institute, in which he took the greatest interest. Literary work took up a good deal of his time. Beside undertaking the very onerous work as editor of the *Biochemical Journal*, he wrote the article on 'Fermentation' for Thorpe's *Dictionary of Chemistry*, the section on 'Yeast enzymes' for Oppenheimer-Pincussen's *Die Fermente und ihre Wirkungen*, and the section on alcoholic fermentation, 'The early stages of fermentation in the yeast cell', for *Die Ergebnisse der Enzymforschung* [Leipzig, 1932]; he was the author of *Alcoholic Fermentation* in the Longmans series of Biochemical Monographs, of which four editions have already appeared, and of the article on 'Bacterial Metabolism in the System of Bacteriology' published by the Medical Research Council [1930].

He was an excellent Committee member, and as editor was a member of the Committee of the Biochemical Society for more than 25 years. He also served on the Council of the Chemical Society, of which he became a Vice-President, and was for some years a member of the Research Fund Committee of the Institute of Brewing, and from 1930 to 1938 Chairman of that Institute's Advisory Committee on Yeast.

Biochemists owe much to Harden not only for the part he took in opening up a large field of new and important work but also for his efforts in securing the recognition of the science of biochemistry in this country. He was one of the founders of the Biochemical Society in 1911, and when in 1912 that Society acquired from Prof. Benjamin Moore the proprietorship of the *Biochemical Journal*, Harden accepted with Bayliss the office of editor. The latter, however, consented to act as joint editor only on condition that he should not be asked to do proof reading, and until the death of Bayliss, twelve years later, the whole brunt of this most arduous work fell on Harden. In 1924 H. W. Dudley became joint editor to be succeeded in 1930 by C. R. Harington, and in this period the

work was more equally divided. In 1938, after Harden had acted as editor for 25 years, the Society expressed their appreciation of the debt they owed him by presenting him with a silver salver on which were engraved the signatures of all the Committee members of the Biochemical Society who had served with him. The success of the *Journal* and the appreciation of his colleagues were for many years the only reward of his unselfish work. It was indeed a notable contribution to the development of the science of biochemistry in this country. He attended meetings of the International Congress of Chemistry, playing an important part on the Committee for the Reform of Biochemical Nomenclature.

Harden had many interests. He kept in touch with his old Manchester friends and students, amongst them Dr H. G. Colman, Prof. S. P. Bedson, Sir Philip Hartog and Sir John Russell. He was a delightful friend, always cheerful and with a dry sense of humour. He read widely and was well versed in the works of the Victorian novelists, liking especially Dickens and Trollope. He enjoyed visits to the theatre and opera, rather as pleasant social functions than because of any deep interest in drama or music. In his later years he was fond of travel and made tours to Greece and Spitzbergen and went with the British Association to South Africa in 1935, keeping on each occasion a notebook in which his doings were recorded and objects of interest were tersely described.

He was an excellent skater, and when a hard frost set in was not expected in the laboratory. In his earlier days at the Lister Institute, with several of his colleagues he joined the Wimbledon Park Golf Club, and many friendly matches were arranged in which Harden's somewhat unorthodox stance used to come in for criticism. During the war of 1914–18 he joined the Volunteer Reserve, and his leisure was spent in digging trenches and in other military exercises. After the war he never returned to golf, but took exercise in gardening. Outside his work his greatest interest was in his garden, and in the summer he generally came to the Institute with some choice bloom in his buttonhole. He was a Fellow of the Horticultural Society, a regular attendant at their flower shows, and his knowledge of flowers was extensive. With his colleagues, Ledingham, Arkwright and Robison, Harden took the keenest interest in the *Observer* acrostics. Every Monday morning, notes were compared, and if a solution was incomplete or dubious, plans were laid for more serious inquiry before the last post on Wednesday.

Harden was a man of methodical habit and of even temperament, knowing neither the heights nor depths of emotion. His philosophical outlook, sound judgement and critical instinct were much valued by his colleagues, and when his advice and help were asked they were readily given, but he was a man whom it was difficult to know intimately. His outlook on life was detached, and he once said of himself at a time of personal sorrow that he had never known what it was to be elated or depressed. His friends regarded him as a man to be thoroughly liked, trusted and respected. His students found him always pleasant to work with and sometimes unexpectedly encouraging when difficulties arose. In some respects he resembled the typical idea of the Englishman, showing neither enthusiasm nor emotion and performing as a matter of course what seemed to him to be his duty, without thought of reward, even when this involved much personal labour freely given. He preferred to be rather an onlooker than a participant in a struggle, and this detachment probably prevented him from entering into closer relations with his students and fellow-workers.

In 1900, he married Georgina Sydney (daughter of Mr C. W. Bridge of Christchurch, New Zealand) who died in 1928. They lived for some time at Richmond and later moved to Bourne End, and at both places his friends and students were entertained to pleasant river excursions in the summer.

In 1930 he retired from his Professorship at the Lister Institute but continued to come every day to his laboratory carrying on experimental work and correcting proofs until a year or two before his death. Towards the end of his life he suffered from a progressive disease from which release came before it had become too irksome and while he still enjoyed his garden, his books and his interest in science.

IDA SMEDLEY-MACLEAN

ROBERT ROBISON

(1883–1941)

It is sad to record the death of Robert Robison who died suddenly in his 58th year. His friends in the Biochemical Society and his colleagues at the Lister Institute are left to mourn the loss of a man of rare charm and fine character.

Robison was born at Newark-on-Trent in 1883 and obtained his early education at the Magnus Grammar School in his native town. He entered University College, Nottingham, in 1900 and attended the usual course of study for an honours degree in chemistry. A breakdown in health, however, caused him to postpone his final examination, and he actually commenced research some time before he finally graduated B.Sc. with honours in chemistry. For two years he investigated the organic compounds of silicon under the direction of Prof. F. S. Kipping, and as a result of this work, which was mainly on benzyl and benzylmethyl derivatives of silicon [Robison & Kipping, *J. Chem. Soc.* 1908, **93**, 439], he was awarded, in 1907, an '1851 Exhibition' Scholarship. The next two years were spent in the laboratory of Prof. Hantzsch at Leipzig, where Robison carried out investigations bearing on the relationship between the colour and constitution of organic compounds. The results of these researches were embodied in two papers [Hantzsch & Robison, *Ber. dtsch. chem. Ges.* 1910, **43**, 45, 92], and the degree of Ph.D. [*summa cum laude*] was awarded to him for his thesis entitled 'Über die polychromen Salze aus Dimethyl und Diphenyl-Violursäure'.

A fellow-student in Leipzig at that time tells us that Robison appeared to enjoy every minute of this stay there. He was fond of music, visited the *Gewandhaus* frequently, and made a special point of being present in the Opera House when his favourite works were given. Being a keen walker he made many excursions during the vacations to other parts of Germany, Austria, Italy and Switzerland.

Robison returned to England in the summer of 1909, and for some months worked in the laboratory of the Nottingham City Analyst, but towards the end of the year he was appointed lecturer and demonstrator in chemistry at University College, Galway. Here much of his time was taken up with plans and arrangements for new laboratories, and although he started work on possible methods for the synthesis of acridines, in collaboration with the late Prof. Senier, he did not complete the investigation, as in October 1910 he was appointed to the post of lecturer and demonstrator in chemistry at University College, Nottingham. The work on organic compounds of silicon was resumed in collaboration with Prof. Kipping, and during the next three years four publications on this subject appeared [*J. Chem. Soc.* 1912, **101**, 2142, 2156; 1914, **105**, 40, 984].

Robison was appointed an assistant in the Biochemical Department of the Lister Institute of Preventive Medicine in March 1913, and here he made his first contact with biochemical problems. He remained a member of the Institute's